Microencapsulation Technology

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INTRODUCTION

Microencapsulation technology has been used from 1930s in packaging flavors and vitamins. Since the first commercial product was introduced for the carbonless copying paper,[1] the technology has advanced to a new level. Various microencapsulation techniques are available nowadays, and the microencapsulated products are widely used in pharmaceutical, biomedical, agricultural, food, consumer products, and cosmetic industries. Representative applications of microparticles in the pharmaceutical and biomedical industries include:

- Taste and odor masking[2]
- Protection of drugs from the environment[3]
- Particle size reduction for enhancing solubility of the poorly soluble drugs[4]
- Sustained or controlled drug delivery[5]
- Cell encapsulation[6]

The microparticle system has become an indispensable part of the controlled drug delivery fields for the past few decades since it can readily be adapted for various administration methods. In particular, biodegradable polymeric microparticles can provide a number of advantages over conventional parenteral formulations:

- *Sustained delivery*: By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug until the time of degradation, microparticles maintain the blood level of the drug within a therapeutic window for a prolonged period. Toxic side effects can be minimized, and patient compliance can be improved by reducing the frequency of administration.
- *Local delivery*: Subcutaneously or intramuscularly applied microparticles can maintain a therapeutically effective concentration at the site of action for a desirable duration. The local delivery system obviates systemic drug administration for local therapeutic effects and can reduce the related systemic side effects. This system has proven beneficial for delivery of local anesthetics.[7]
- *Pulsatile delivery*: While burst and pulsatile release is not considered desirable for the sustained delivery application, this release pattern proves to be useful for delivery of antibiotics and vaccines. Pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulses can mimic an initial and boost injection, respectively.[8]

With the recent advance of biotechnology and polymer chemistry, the use of microparticle systems will continue to grow for a variety of applications. The objective of this article is to provide a review of the technical aspects of the microencapsulation techniques that have been widely used in the pharmaceutical industry and recent advances of the technology so that the pharmaceutical scientists can take full advantage of the existing assets of this area in developing new microparticle systems.

TERMINOLOGY

The microencapsulation processes produce small particles ranging in size from 1 to 1000 μm. There are different names for these particles: microparticle, microsphere, microcapsule, and micromatrix. Although they are often used interchangeably, distinctions can be made such that microcapsules are made of one or multiple core substances (solid or liquid) that are surrounded by a distinct capsule wall, whereas micromatrices are polymeric matrices in which the encapsulated substances are homogeneously dispersed. Microparticles or microspheres are general terminologies that involve both. Although micromatrices are also called microspheres depending on the authors,[5] we will follow the former definition in this chapter. In consideration of the scope of this chapter, current discussion is limited to the microparticles that utilize natural or synthetic polymers as an encapsulating material.

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MICROENCAPSULATION TECHNIQUES

Existing microencapsulation techniques have been reviewed extensively,[5,9–13] and for this reason, here we will briefly summarize representative microencapsulation techniques.

Coacervation

The coacervation method is one of the earliest microencapsulation techniques, which has been used for various consumer products. This method is based on separation of a solution of hydrophilic polymer(s) into two phases, which are small droplets of a dense polymer-rich phase and a dilute liquid phase. Coacervation can be divided into simple and complex coacervation depending on the number of polymers that are involved in the formation of microparticles.

Simple coacervation

This process involves only one polymer (e.g., gelatin, polyvinyl alcohol, carboxymethyl cellulose), and the phase separation can be induced by conditions that result in desolvation (or dehydration) of the polymer phase. These conditions include addition of a water-miscible non-solvent, such as ethanol, acetone, dioxane, isopropanol, or propanol,[1,3] addition of inorganic salts, such as sodium sulfate,[1,4] and temperature change.[5]

Complex coacervation

This process involves two hydrophilic polymers of opposite charges.[1,3] Neutralization of the overall positive charges on one of the polymers by the negative charge on the other is used to bring about separation of the polymer-rich phase (Fig. 1). The best-known example is the gelatin-gum arabic system pioneered by Bungenberg de Jong in the early 1940s.[16] Since electrostatic interactions are involved, the pH of the medium is very important. For example, in the gelatin-gum arabic system, pH should be below the isoelectric point of gelatin so that the gelatin can maintain the positive charge. Once embryonic coacervates form around the dispersed oil or solid phases, these polymer complexes are stabilized by cross-linking using glutaraldehyde.

Commercial products

The first commercial microparticle product based on the complex coacervation method was carbonless copy paper developed by National Cash Register Corp.[1] The back side of the first page is coated with microcapsules in the 3–10 μm size range made of a gelatin-gum arabic shell by the coacervation technique. In the center of the capsules is the oil containing colorless color-forming agent (e.g., crystal violet lactone). The front side of the second page is coated with a developing layer. The pressure imposed on both sheets of paper upon writing induces breakage of the microcapsules and makes the colorless color-forming agent released and react with the developing layer to develop color. The microcapsules have also been used in Scratch-N-Sniff® scent strips and Snap-N-Burst® fragrance samplers.

Emulsion Solidification

Microparticles can be produced from emulsion of two or more immiscible liquids. For example, a

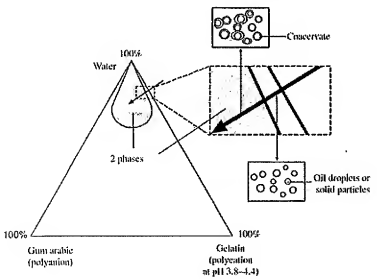

Fig. 1 Phase diagram for complex coacervation.

hurdles are maintaining the stability of encapsulated drugs throughout the lifetime of the products, manipulating release rates according to the applications, and transferring bench scale processes to the manufacturing scale. Some of the answers to those problems have been provided by advances in polymer chemistry, formulation efforts, and recent progresses in new microencapsulation techniques. The microencapsulation technology will remain as one of the most important areas in drug delivery and various other applications.

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ARTICLE OF FURTHER INTEREST

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